PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61L 27/00, 33/00, A61F 2/24 — A1

(11) International Publication Number: WO 96/30060

(43) International Publication Date: 3 October 1996 (03.10.96)

(21) International Application Number: PCT/GB96/00725

(22) International Filing Date: 27 March 1996 (27.03.96)

(30) Priority Data:
9506769.0 28 March 1995 (28.03.95) GB

(71) Applicant *(for all designated States except US)*: AORTECH EUROPE LTD. [GB/GB]; Strathclyde Business Park, Bellshill, Strathclyde ML4 3NJ (GB).

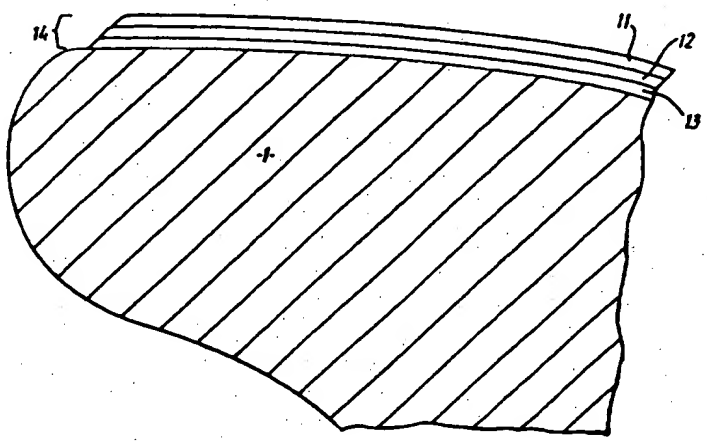
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: McDAID, Edward [GB/GB]; 5 Sweethope Gardens, Bothwell, Glasgow G71 8BT (GB). WRIGHT, James, Gordon [GB/GB]; 17 Lady Jane Gate, Bothwell, Glasgow G71 8BW (GB).

(74) Agent: MURGITROYD & COMPANY; 373 Scotland Street, Glasgow G5 8QA (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: MEDICAL DEVICE TREATED WITH A HYDROPHILIC POLYMER COMPOSITION



(57) Abstract

There is provided medical devices for use as cardiac, coronary or vascular prostheses, for example heart valves, coronary artery bypass grafts and arterial grafts. The devices described are at least partially coated or impregnated with a hydrophilic polymer composition which desirably contains of from 1 to 99 % by weight of water, preferably 50 to 95 % by weight of water. The hydrophilic polymer composition may be biodegradable and preferably contains a polyurethane. Optionally the hydrophilic polymer composition may contain a pharmaceutically active agent, for example an anti-coagulant, a thrombolytic agent or an antibiotic. The device may be treated with two or more hydrophilic polymer compositions in separate coatings; a triple-layered coating may be especially beneficial. The presence of the hydrophilic polymer coating is beneficial in reducing the thrombogenesis which may occur following implantation of the device

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia
AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

"Medical Device Treated with a Hydrophilic Polymer Composition"

The present invention relates to medical implants and equipment having a hydrophilic polymer composition coating. In particular, the present invention is concerned with cardiac implants and vascular prostheses.

In mammals the heart is a vital organ responsible for maintaining an adequate flow of blood (and hence oxygen and nutrients) to all parts of the body. Essentially the heart acts as a mechanical pump, forcing the blood delivered to it via veins out along arteries at higher pressure. The blood is prevented from flowing backwards through the heart by the presence of valves located therein.

Dysfunction of one or more of the valves in the heart can have serious medical consequences. Dysfunction of heart valves may be the result of a congenital defect, or of disease-induced damage or degeneration. Dysfunction frequently results from stenosis or narrowing of the valve aperture, preventing sufficient blood through-flow. Further, dysfunction also

frequently results from valve insufficiency. In addition to cardiac valve replacement operations, operations for coronary bypass are also frequently required.

To date, the only solution to treat severe heart valve dysfunction is to replace the malfunctioning valve. Such a valve replacement operation, in addition to being extremely costly, requires complex open-heart surgery. There is a also a finite number of times that a heart valve can be replaced successfully for any particular patient, making the design and operational lifetime of any replacement valve extremely important.

Mechanical valves have been developed and used for heart valve replacement operations. Whilst such valves exhibit excellent operational lifetimes, they suffer from a higher incidence of thrombosis (blood clotting) due to the trigger of clotting in the blood as the material of the valve is recognised by the immune system as being "foreign" to the body. Suitable heart valves are manufactured, for example, by Aortech Europe Limited, Strathclyde, UK under the name ULTRACOR (Trade Mark). Heat valves manufactured by St Jude Medical, CarboMedics, Medtronic or ATS Medical, USA are all suitable as are valves manufactured by Sorin, Italy

Currently mechanical valve implants are estimated at 110,000 implants worldwide with an average price of between US$2,000 and $3,000 retail to the hospital. The one major clinical problem facing mechanical valves is anti-coagulation. It is currently believed that the majority of emboli and clots initially grow from the junction of the sewing ring with the metal or pyrolite housing. Also suture material and large knots put in

place when the surgeon implants the valve may be the cause of some of these phenomena. Currently no manufacturer has an anti-thrombogenic coating on their valves and the ability to do this with the consequent lowering of the frequency of embolic episodes or the more catastrophic thrombosis which can lead to death of the patient would be highly desirable.

In an effort to reduce the risk of thrombosis to a patient, it has been proposed (see for example EP-A-0,402,036 of ProMedica International Inc) to use porcine pulmonary valves in human patients. Surprisingly such xenografts show less tendency to be destroyed by the recipient, especially where the donor organ has been pre-treated with glutaraldehyde to reduce the risk of calcification. However, such valves have a finite lifetime and must generally be replaced within 10 years of implantation.

With increasing life expectancy for humans, there is a corresponding rise in patients requiring cardiac valve replacement and/or coronary bypass operations. There is thus an increasing need for cardiac and vascular prostheses having both an extended useful lifetime and also a low risk of inducing thrombosis in a recipient.

It has now been found that coating or impregnating at least part of a cardiac prosthesis (such as a heart valve) with a hydrophilic polymer composition significantly reduces thrombogenesis.

The present invention thus provides a cardiac, coronary or vascular prosthesis having a coating of hydrophilic polymer composition on at least a part thereof and/or being at least partially impregnated with a hydrophilic polymer composition.

Viewed from a further aspect the present invention provides a heart valve wherein at least part of the valve (for example the sewing ring and/or the junction of the sewing ring with the heart valve housing) is coated or impregnated with a hydrophilic polymer composition.

Viewed from a yet further aspect the present invention provides a prosthesis (for example coronary artery bypass grafts and arterial grafts) suitable for coronary bypass operations and vascular surgery wherein at least part of the surface to be contacted by bodily fluids (preferably substantially all of such surfaces) is coated or impregnated with a hydrophilic polymer composition.

In coronary bypass operations surgeons currently harvest the saphenous vein from the patient's leg, which often causes the patient post-operatively more pain problems than the thoracotomy. It is estimated that after ten years a significant number of all coronary artery bypass grafts are either grossly inefficient at providing extra blood flow to the ischemic part of the heart or have completely clotted and closed down. An artificial coronary artery bypass graft, which would be coated or impregnated completely with an anti-thrombogenic material would be desirable despite the fact that vein grafts are harvested free.

Where the prosthesis is a mechanical heart valve, the hydrophilic polymer composition may be present on the sewing ring thereof and/or on the junction of the sewing ring with the metallic part of the valve housing, Suitable sewing ring material which may be coated according to the present invention includes T flon.

Optionally, the hydrophilic polymer composition may coat or be used t impregnate substantially all of the surfaces of the coronary prostheses or vascular grafts.

The hydrophilic polymer composition may contain of from 1% to 99% water (by weight), for example said composition may contain 20% to 99% water, especially 40 to 95% water. The composition will normally be liquid at ambient temperature and may be sprayed or painted onto the device of the present invention. Alternatively the device may be dipped into the composition and allowed to dry thereon.

Desirably, the hydrophilic polymer has low surface adhesion properties, thus reducing the incidence or risk of thrombogenesis.

Suitable hydrophilic polymers are described in US-A-4,256,066; US-A-4,156,067; US-A-4,255,550;; US-A-4,359,588; US-A-4,408,023; US-A-4,424,305; US-A-4,490,432; US-A-4,496,535; US-A-4,729,914; US-A-4,743,673; US-A-4,780,512; US-A-4,789,720; US-A-4,798,876; US-A-4,810,582; US-A-5,000,955 and US-A-4,789,720 all of Tyndale Plains Hunter Ltd, Princeton, New Jersey.

In particular, the hydrophilic polymers may be polyurethanes, as described in US-A-5,120,816 and in US-A-4,789,720. The polymers exemplified in US-A-4,789,720 and in US-A-5,120,816 are especially suitable.

The advantageous biomedical properties of certain hydrophilic polymers suitable for use in the present invention (for example as disclosed in US-A-4,789,720 and in US-A-5,120,816) derive from the structure of the

polymers which are prepared by reacting an aliphatic diisocyanate with different polyoxyalkylene glycols, usually with a majority of polyoxyethylene glycol. The polymers contain terminal hydroxyl groups and can be made to different molecular weights and degrees of hydrophilicity by adjusting the ratio of hydrophilic to hydrophobic glycol. The hydrophilicity of these polymers can be varied over a wide range, from extremely hydrophilic to hydrophobic polymers as required. Preferably, the polymer composition contains of from 50 to 95% water. The polymer will normally have an average molecular weight range of about 10,000 to 200,000.

In one embodiment, the hydrophilic polymers are biodegradable. Mention may be made of the polyurethane polymers of US-A-4,789,720 and of US-A-5,120,816 which are degraded over time to produce urea, which is then excreted from the body in urine. The time taken for the polymer to be degraded and thus the operational lifetime of the polymer composition may be varied by adjusting or modifying the chemical nature of the polymer structure. Such modification can be carried out during manufacture of the polymer, or may be a post-production modification to the polymer.

Alternatively, a polymer which is viewed as non-biodegradable within the art may be used and this may be preferred in certain aspects.

In a further embodiment, the hydrophilic polymer composition may be used as a carrier for pharmaceutically active agents. Suitable agents include immuno-suppressant drugs (to reduce the risk of prosthesis rejection or to combat such rejection reaction); anti-bacterial agents, such as antibiotics

(to reduce the risk of infection or to combat infection introduced during the operation to implant the prosthesis), growth factor regulators and anti-coagulant, anti-thrombogenic or thrombolytic drugs (to reduce the risk or to combat thrombosis and emboli formation). Mention may be made of heparin, heparin fragments tissue-type plasminogen activator (tPA), urokinase (uPA), anti-thrombosis agents (such as Hirudan) and albumin, as examples of suitable anti-coagulant agents to combat thrombosis. Also suitable are anti-coagulant agents which are antibodies (for example antibodies directed against platelet receptor GPIb and/or GPIb, against platelet receptor GPIIb/IIIa, and/or against von Willebrand Factor (vWF)) and also such agents with vasoactive properties (such as Prostacyclin and Nitric Oxide). With regard to pharmaceutically active agents which act as growth factor regulators particular mention may be made of antibodies, such as antibodies directed against Platelet-derived Growth Factor (PDGF), Fibroblastic Growth Factor (FGF), Transforming Growth Factor beta (TGF), Insulin-like Growth Factor (IGF), Interleukins (IL1-8), Endothelin, Thrombin, and/or Endothelial adhesion molecules eg ICAM-1. Also suitable are angiotensin converting enzyme (ACE) inhibitors (for example Captopril), and endothelial cell growth factor (ECGF). In certain aspects use of anti-sense oligonucleotides or antibodies to particular mRNAs may be advantageous, for example anti-sense oligonucleotides to a -myc, PCNA and the like or antibodies to the mRNA molecules encoding for growth factors.

Suitable antibiotics which may advantageously be present in the polymer of the invention include Penicillins, Cephaolsporins, Aminoglycosides,

Tetracyclines, Macrolides, Glycopeptides eg Vancomycin, Teicoplanin, Sulphonamides and/or Anti-fungals eg Fluconazole. More than one pharmaceutically active agent may be present.

The pharmaceutically active agent may be chemically bound (for example via a covalent or ionic bond) to the hydrophilic polymer. Alternatively, the pharmaceutically active agent may be physically entrapped within the polymer and released as the polymer degrades in the body.

In certain instances it may be desirable to have more than one coating on said prostheses. Thus, for example the hydrophilic polymer (optionally comprising a pharmaceutically active agent) may itself be coated, for example with a delay release coating or more preferably may itself be coated with a further coating of hydrophilic polymer.

In an analogous manner, there may be three or more different layers of hydrophilic polymer coatings. Each layer may be of the same or different chemical composition (ie chemical structure of the hydrophilic polymer and/or water content thereof) and may contain the same or different amounts of identical or distinct pharmaceutically active agent(s). By careful selection of the layers used to coat a prosthesis, the lifetime of the polymer coatings and/or release of any pharmaceutically active agent comprised therein may be controlled.

For example a triple-layer coating may be desirable. The first coating immediate to the prosthesis may optionally comprise an agent which is released only slowly, the first coating layer being degradable very

slowly over time. Instead of a first coating layer, the prosthesis may be impregnated with such a hydrophilic polymer composition. An intermediate coating may then be coated over said first layer, the intermediate layer having a lifetime of approximately 6 weeks and an appropriate amount of pharmaceutically active agent. The top layer covering said intermediate layer may be designed to release an amount of anti-thrombogenic agent over the danger period (extending for approximately 10 days) for producing blood clots and emboli; this being the lifetime of the top layer once in the body.

Viewed from a further aspect, the present invention provides a method of treating prostheses to reduce the risk (and incidence) of thrombogenesis after implantation in a patient, said method comprising treating at least a part of said prostheses with a hydrophilic polymer composition. Generally, said prostheses may be impregnated and/or coated with said polymer by any suitable conventional means. Mention may be made of producing a polymer film which is then adhered to the prostheses or, more usually, forming said polymer on said prostheses in situ.

Viewed from a yet further aspect the present invention provides a method of treating cardiac and vascular dysfunction in a patient, said method comprising implanting coronary prostheses coated and/or impregnated with a hydrophilic polymer composition as hereinbefore described.

In a yet further aspect the present invention provides the use of prostheses coated and/or impregnated with a hydrophilic polymer composition (especially a mechanical heart valve, coronary artery bypass grafts

and arterial grafts) for implantation in a patient to relieve cardiac and vascular dysfunction.

In a still yet further aspect the present invention provides the use of a hydrophilic polymer composition as hereinbefore described to coat and/or impregnate cardiac, coronary or vascular prostheses.

Viewed from another aspect the present invention provides the use of a hydrophilic polymer composition as hereinbefore described in the manufacture of cardiac, coronary or vascular prostheses for implantation in a patient to relieve coronary or vascular dysfunction.

Figure 1 is a schematic view in partial cross-section of a conventional heart valve prosthesis.

Figure 2 is a detailed cross-section of the junction between the sewing ring and heart valve housing of the heart valve prosthesis shown in Figure 1 following implantation into a patient.

Figures 3 and 4 are schematic partial cross-sections of the conventional heart valve prosthesis of Figure 1 at different stages after implantation in the patient.

Figure 5 is a cross-section giving details of the attachment of a conventional heart valve to patient tissue.

Figures 6 and 7 are cross-sections of the heart valve illustrated in Figure 5 following different periods of implantation in the patient.

Figure 8 is a cross-section of a portion of the sewing

ring of the heart valve following treatment with a hydrophilic polymer composition.

In more detail, Figures 1 to 7 illustrate conventional heart valves as currently used in heart valve replacement surgery. The heart valves illustrated are mechanical prostheses, likely to initiate blood clot formation as shown in Figures 2, 3, 4, 6 and 7. Conventional mechanical heart valve 10 comprise sewing ring 1 which completely surrounds the outer ring of the valve housing 2. There is a junction 3 between the sewing ring 1 and valve housing 2.

As is illustrated in Figure 5 sewing ring 1 is used to attach the mechanical heart valve 10 into the patient by means of sutures, staples or the like. As illustrated, a suture 6 has been used to extend through sewing ring 1 and a flap of patient tissue 5. The suture 6 is securely fastened with knot 7. Alternative means of attachment of the heart valve 10 into the patient may also be used.

Following implantation of mechanical heart valve 10 into a patient, the heart valve 10 is exposed to the patient's immune system and its near presence within the patient may initiate blood clotting as a form of immune reaction. Blood clotting may be initiated in two locations, in particular the junction 3 between sewing ring 1 and valve housing 2 and also surrounding the suture knot 7. Figure 2 illustrates an initial blood clot 4 which has become established at junction 3 between sewing ring 1 and housing 2. The growth of this blood clot is illustrated in Figures 3 and 4. From Figure 4 the blood clot is shown extending vertically down housing 2 and any further increase in size in clot 4 could seriously impair the function of

the replacement valve 10.

Figure 6 illustrates blood clot 4 initially formed at junction 3 between sewing ring 1 and valve housing 2. Additionally a further clot 8 is shown surrounding knot 7 of suture 6. Figure 7 illustrates the growth of blood clots 4, 8 following a further period of time, and as illustrated the clots 4, 8 have merged into a single merged blood clot 9 which extends over housing 2, junction 3 and a large portion of sewing ring 1, including knot 7. The risk that a portion of clot 9 will become detached, thus creating thrombosis or emboli problems within the patient, is high.

Figure 8 illustrates a portion of sewing ring 1 of a conventional heart valve 10 in cross-section and treated with a layer 14 of a hydrophilic polymer composition. As illustrated only a portion of sewing ring 1 has been treated with the hydrophilic polymer composition, and coating 14 extends across the surface of sewing ring 1 which is particularly vulnerable to initiating blood clot formation. In coating 14 the hydrophilic polymer composition is in fact a composite of three separate layers, each containing a different hydrophilic polymer. Layer 11 which is immediately exposed to the patient's immune system is selected to biodegrade over a three day period and comprises an anti-thrombogenic agent and/or an antibiotic which is controllably released over that timescale to combat blood clot and emboli formation. Intermediate layer 12 is designed to biodegrade within a two week period and contains a lesser amount of a pharmaceutically active agent, for example an anti-thrombogenic agent. Layer 13 is designed to biodegrade over a six month time scale. The triple-layer coating illustrated in Figure 8 is a preferred embodiment of the invention since this

arrangement permits a high degree of control immediately following implantation, whilst avoiding unnecessary release of the anti-thrombogenic agent over a much longer timescale, for example over six months. Once coating 14 has completely biodegraded, the patient's immune system will have adapted to the presence of the heart valve 10 and the liklihood of thrombogenesis or emboli formation at that stage is much reduced. Instead of a coating 14, it is also possible for the heart valve 10 to be partially impregnated with a hydrophilic polymer composite.

It is also possible for a single or dual layer hydrophilic polymer composition to be used, rather than the triple-layer coating illustrated in Figure 8.

Likewise other mechanical prostheses for cardiac, coronary or vascular surgery may be impregnated or coated with suitable hydrophilic polymer composition(s).

CLAIMS

1. A cardiac, coronary or vascular prosthesis having a coating of hydrophilic polymer or at a part thereof and/or being at least partially impregnated with a hydrophilic polymer composition.

2. A prosthesis as claimed in Claim 1 wherein at least a part of the surface to be contacted by body fluids is coated or impregnated with siad hydrophilic polymer composition.

3. A prosthesis as claimed in Claim 2 wherein substantially all of the surface to be contacted by body fluids is coated or impregnated with said hydrophilic polymer composition.

4. A prosthesis as claimed in any one of Claims 1 to 3 which is a heart valve.

5. A prosthesis as claimed in Claim 4 wherein the sewing ring and/or the junction between the sewing ring and heart valve housing is coated or impregnated with said hydrophilic polymer composition.

6. A prosthesis as claimed in any one of Claims 1 to 3 which is suitable for coronary bypass operations or vascular surgery.

7. A prosthesis as claimed in Claim 6 capable of use as a coronary artery bypass graft or an arterial graft.

8. A prosthesis as claimed in any one of Claims 1 to

7 wherein said hydrophilic polymer composition contains of from 1% to 99% by weight of water.

9. A prosthesis as claimed in Claim 8 wherein said hydrophilic composition contains of from 40 to 95% by weight of water.

10. A prosthesis as claimed in any one of Claims 1 to 9 wherein said hydrophilic polymer composition comprises a polyurethane.

11. A prosthesis as claimed in any one of Claims 1 to 10 wherein said hydrophilic polymer composition is biodegradable.

12. A prosthesis as claimed in any one of Claims 1 to 11 wherein said hydrophilic polyer composition also contains a pharmaceutically active agent.

13. A prosthesis as claimed in Claim 12 wherein said agent has an anti-coagulant, anti-thrombogenic or a thrombolytic activity.

14. A prosthesis as claimed in any one of Claims 1 to 13 impregnated or coated with two or more hydrophilic polymer compositions which may be the same or different.

15. A prosthesis as claimed in Claim 14 having a triple-layer coating.

16. A method of treating a cardiac, coronary or vascular prosthesis to reduce thrombogenesis following implantation in a paitent, said method comprising treating said prosthesis with a hydrophilic polymer composition.

17. A method as claimed in Claim 16 wherein said hydrophilic polymer composition is as defined in any one of Claims 8 to 13.

18. The use of a hydrophilic polymer composition as claimed in any one of Claims 8 to 13 to coat or impregnate at least a portion of a cardiac, coronary or vascular prosthesis.

19. The use of a hydrophilic polymer composition as claimed in any one of Claims 8 to 13 manufacture a cardiac, coronary or vascular prosthesis for implantation in a patient to relieve coronary or vascular dysfunction.

20. Use as claimed in either one of Claims 18 and 19 wherein said prosthesis is a heart valve.

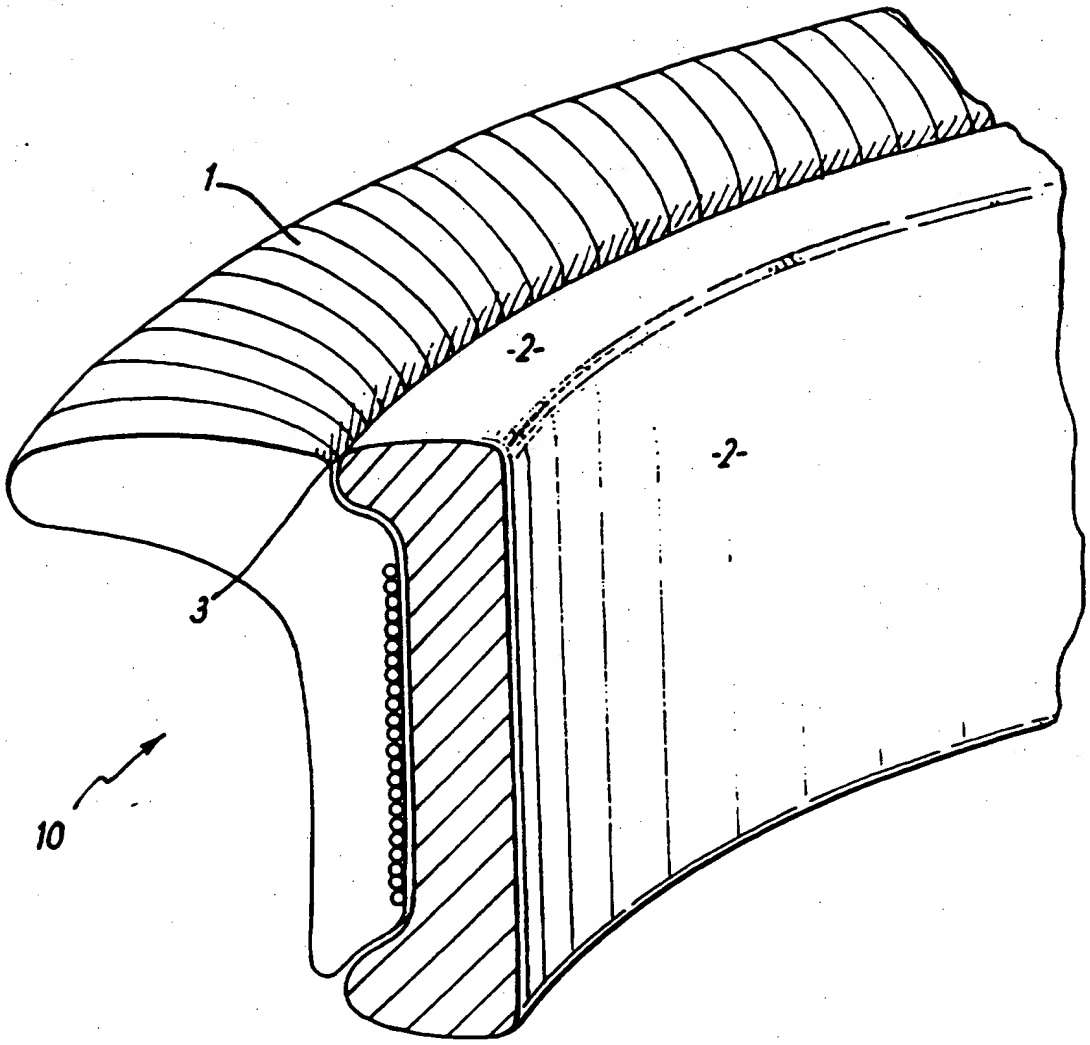


FIG.1

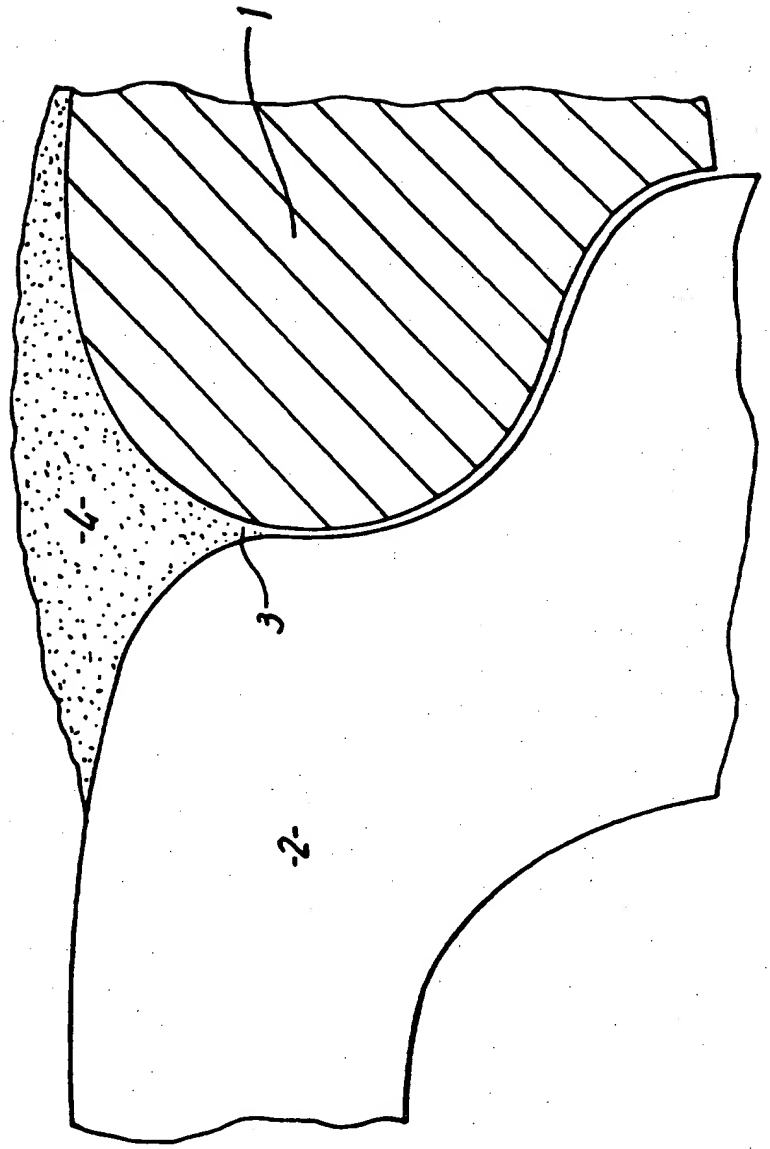


Fig 2

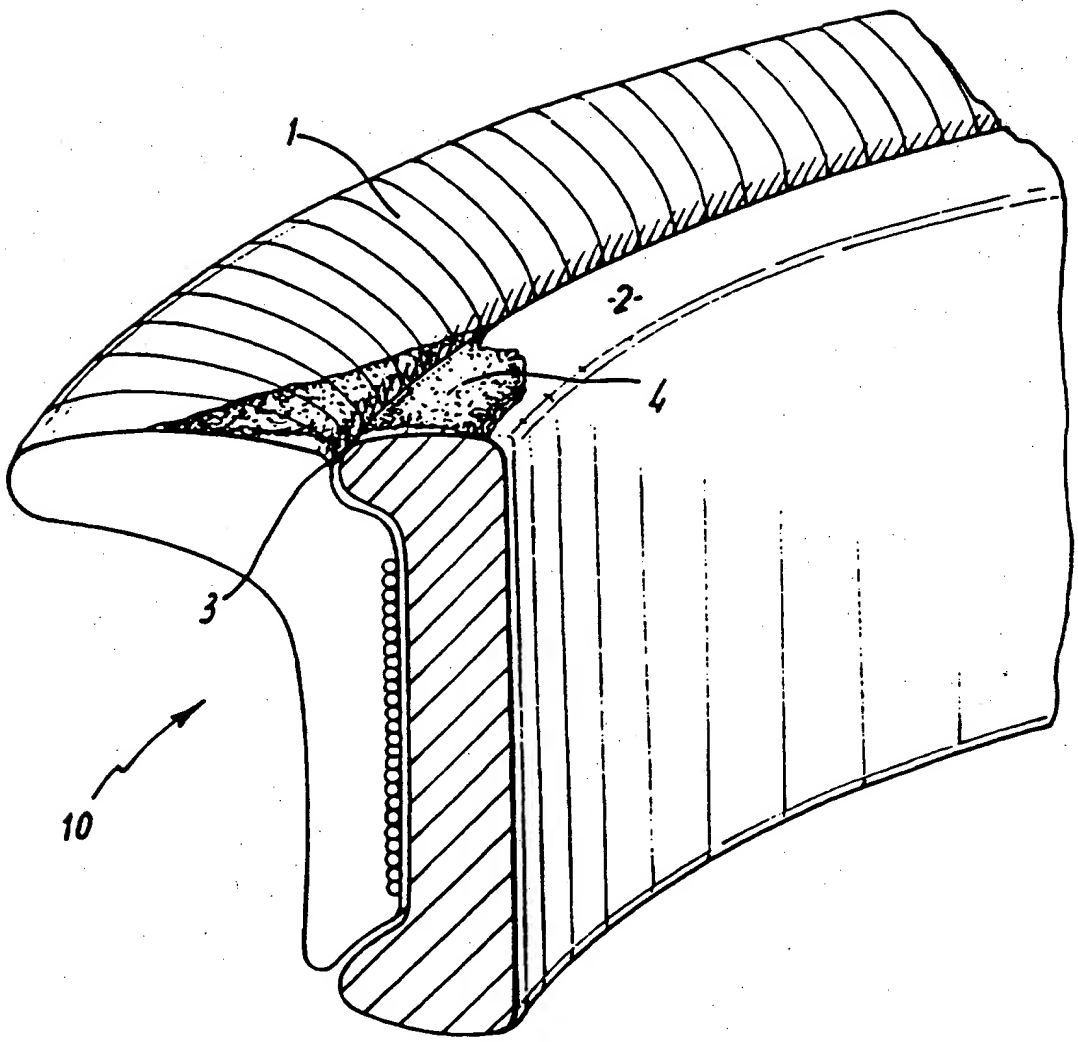


FIG.3

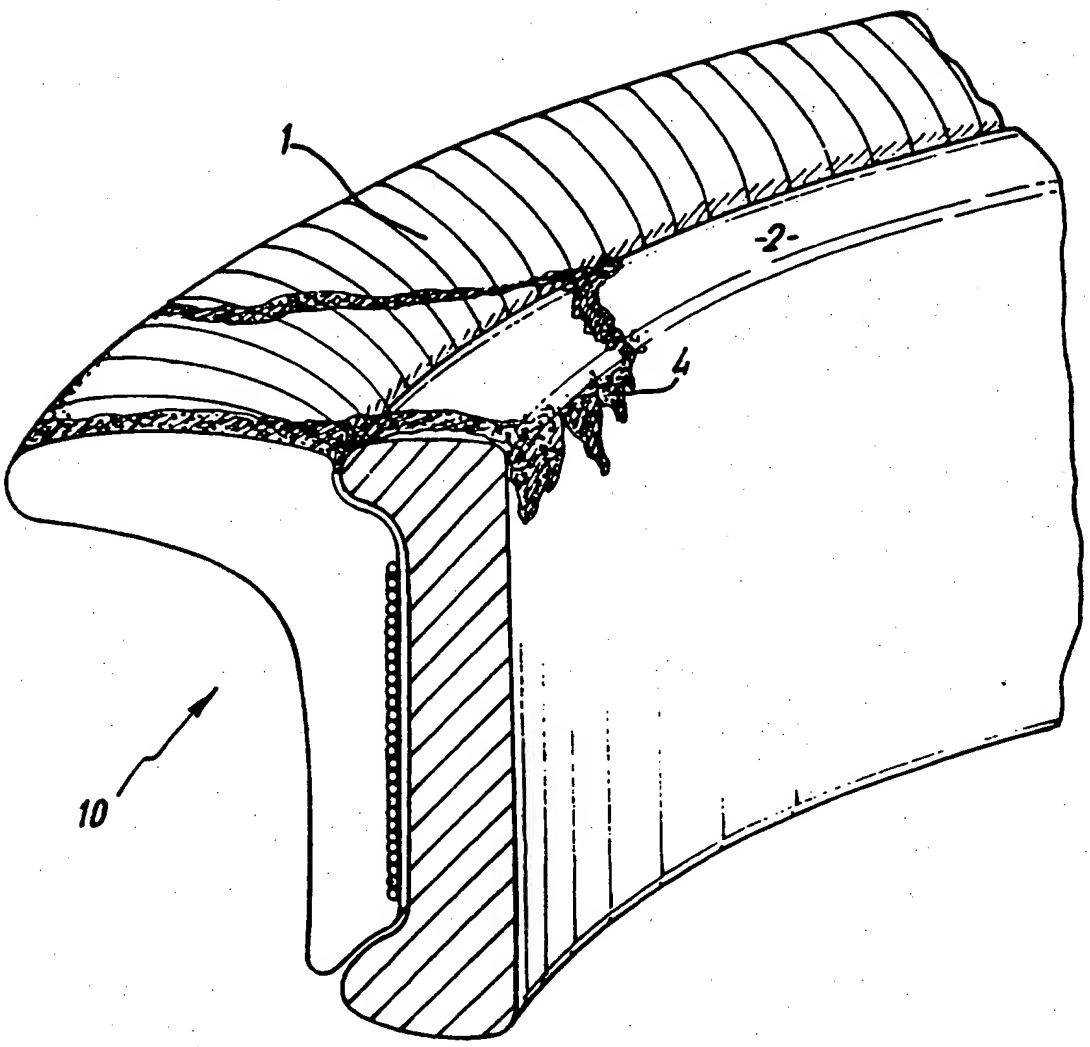


FIG.4

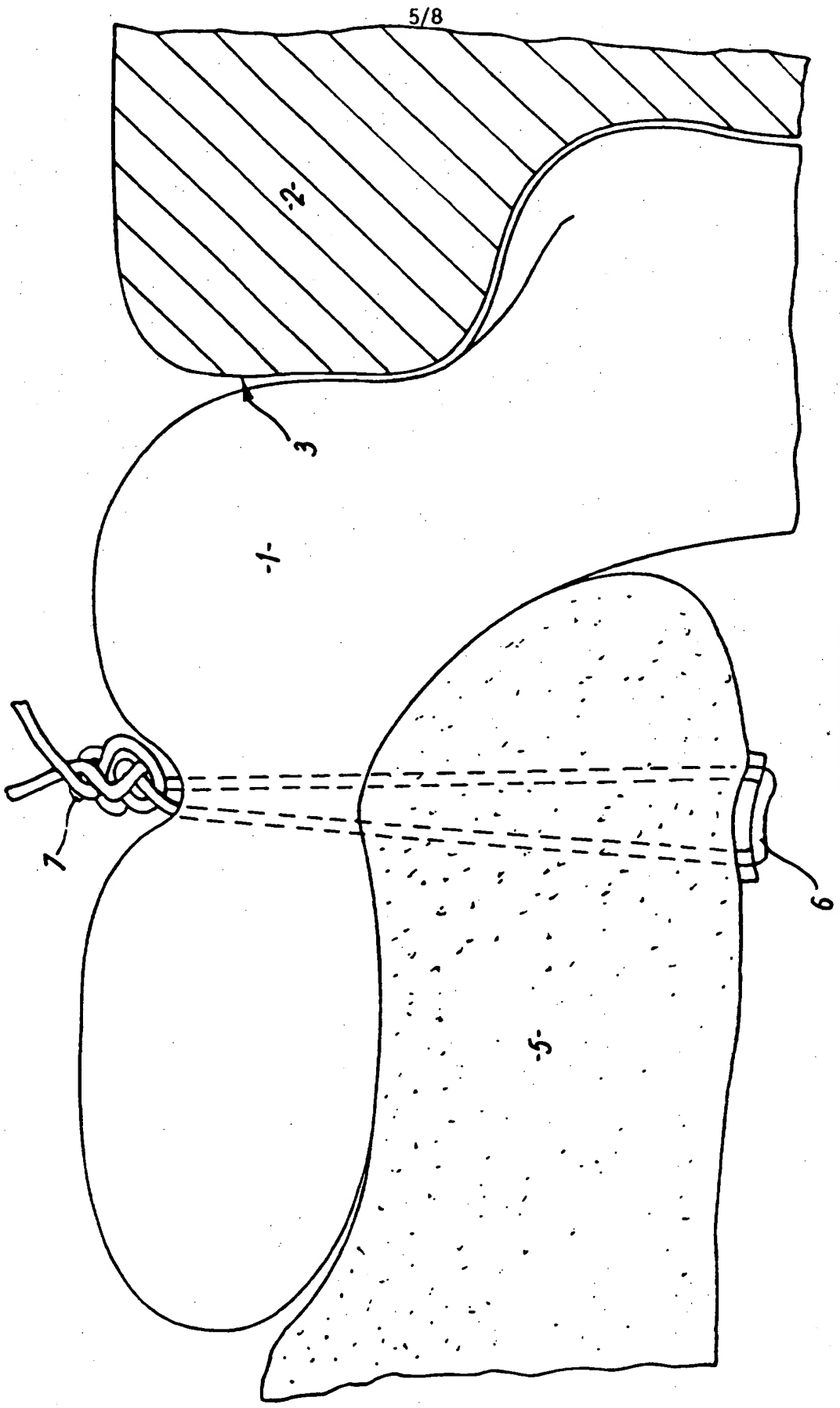


FIG.5

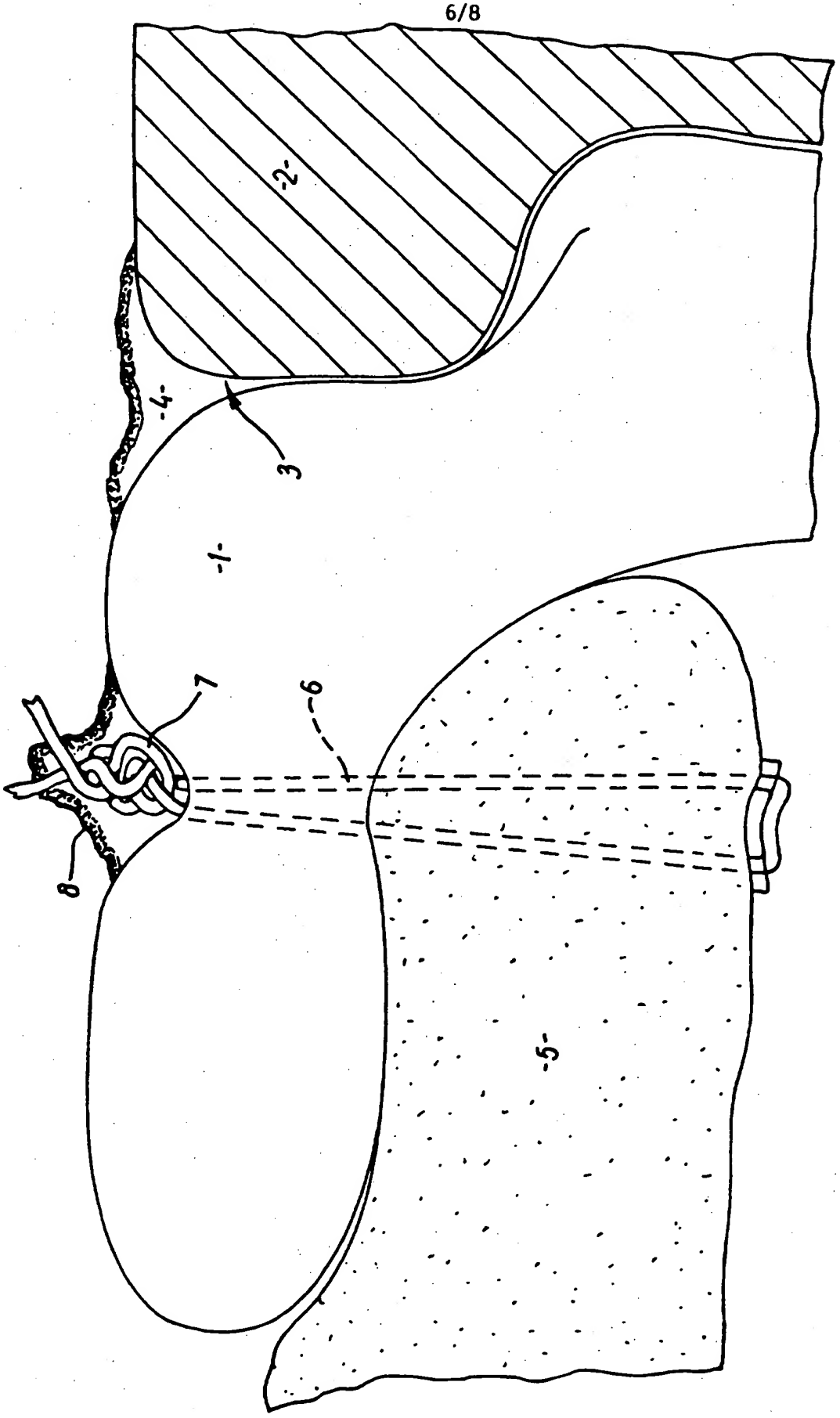


FIG.6

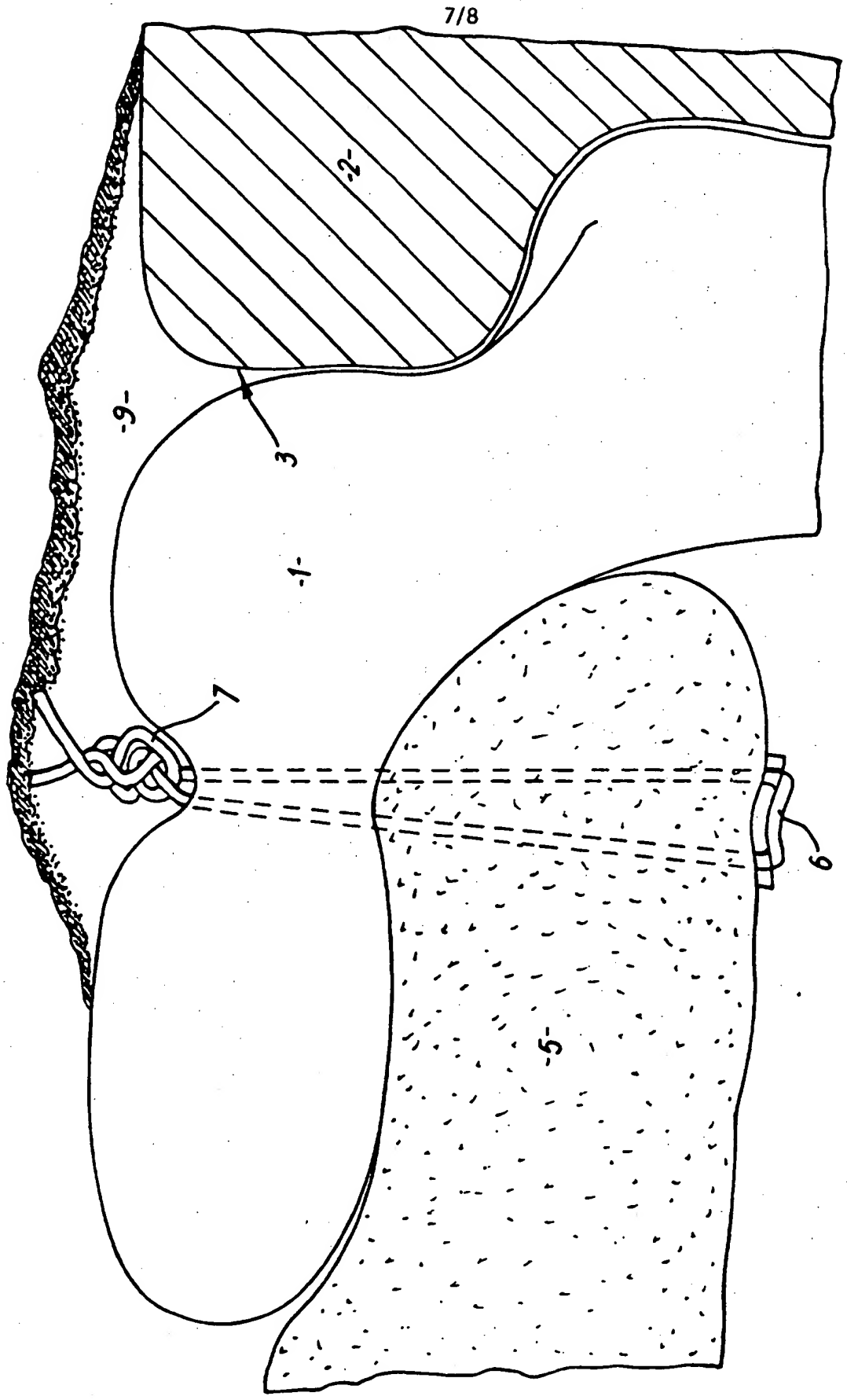


FIG. 7

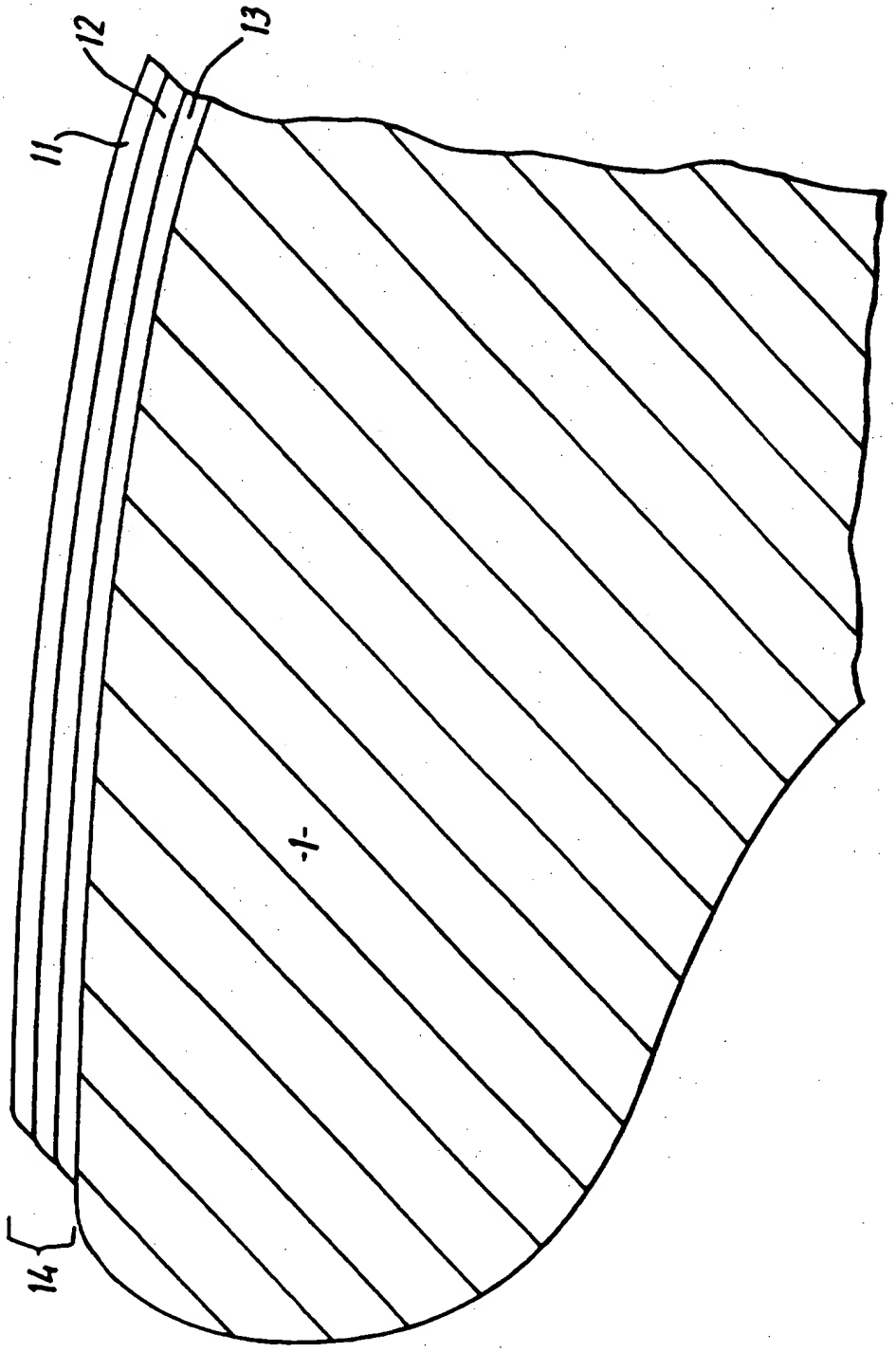


FIG.8

INTERNATIONAL SEARCH REPORT

Inter ~onal Application No
PC1/GB 96/00725

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L27/00 A61L33/00 A61F2/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 21308 (CEDARS SINAI MEDICAL CENTER) 29 September 1994 see page 6, line 15 - line 20; examples 1-4	1-20
X	GB,A,2 255 394 (GALRAM TECHNOLOGY IND LTD) 4 November 1992 see claims	1-3
X	EP,A,0 106 004 (INT SILICONE CORP) 25 April 1984 see the whole document	1-3
Y	WO,A,90 14054 (IMPRA INC) 29 November 1990 see claims	1-20

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
1 August 1996	14.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	ESPINOSA, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/00725

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,4 729 914 (KLIMENT CHARLES K ET AL) 8 March 1988 cited in the application see examples 1-9	1-20
A	EP,A,0 335 308 (GRACE W R & CO) 4 October 1989 see claims	1-20
A	WO,A,89 11500 (COMMW SCIENT IND RES ORG) 30 November 1989 see claims	1-3
A	US,A,4 119 094 (MICKLUS MICHAEL J ET AL) 10 October 1978 see claims; examples 1,2	1
A	EP,A,0 443 993 (SORIN BIOMEDICA SPA) 28 August 1991 see column 3, line 20 - line 28; claims	1-3

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB96/00725

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 16,17
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 16 and 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter onal Application No
PCT/GB 96/00725

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9421308	29-09-94	EP-A-	0689465	03-01-96
GB-A-2255394	04-11-92	DE-A-	4214098	05-11-92
		FR-A-	2675992	06-11-92
EP-A-0106004	25-04-84	US-A-	4373009	08-02-83
		AU-B-	556584	13-11-86
		AU-B-	8947382	03-05-84
		GB-A,B	2128500	02-05-84
		JP-C-	1866555	26-08-94
		JP-B-	3077819	11-12-91
		JP-A-	59081341	11-05-84
WO-A-9014054	29-11-90	US-A-	5152782	06-10-92
		DE-D-	69024212	25-01-96
		EP-A-	0473694	11-03-92
		JP-T-	4505720	08-10-92
US-A-4729914	08-03-88	DE-A-	3708954	06-10-88
		FR-A-	2612120	16-09-88
		GB-A-	2202762	05-10-88
		JP-A-	63238170	04-10-88
EP-A-0335308	04-10-89	DE-D-	68911181	20-01-94
		DE-T-	68911181	07-04-94
		JP-A-	1310665	14-12-89
		US-A-	5169720	08-12-92
WO-A-8911500	30-11-89	NONE		
US-A-4119094	10-10-78	US-A-	4100309	11-07-78
		AR-A-	219763	15-09-80
		AU-B-	512679	23-10-80
		AU-B-	3856878	05-06-80
		BE-A-	869588	01-12-78
		CA-A-	1109344	22-09-81
		CH-A-	639675	30-11-83
		CH-A-	634590	15-02-83
		DE-A-	2828617	01-03-79
		FR-A,B	2399879	09-03-79

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 96/00725

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4119094		GB-A-	1600963	21-10-81
		JP-C-	1246290	25-12-84
		JP-A-	54029343	05-03-79
		JP-B-	59019582	07-05-84
		NL-A-	7808290	12-02-79
		SE-B-	441064	09-09-85
		SE-A-	7808442	10-02-79
EP-A-0443993	28-08-91	IT-B-	1240111	27-11-93
		DE-D-	69101458	28-04-94
		DE-T-	69101458	14-07-94
		ES-T-	2050521	16-05-94
		US-A-	5163954	17-11-92